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10/586,345	07/14/2006	Johannes Reinmuller	WEICKM-0061	2694

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EXAMINER	
GOON, SCARLETT Y	
ART UNIT	PAPER NUMBER
1623	
MAIL DATE	DELIVERY MODE
04/14/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/586,345	REINMULLER ET AL.	
	Examiner	Art Unit	
	SCARLETT GOON	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 February 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13 and 22-24* is/are pending in the application.

4a) Of the above claim(s) *7,8,10,22 and 24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,9,11-13 and 23* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *25 February 2009*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This Office Action is in response to Applicants' Amendment and Remarks filed on 25 February 2009 in which claims 14-21 were cancelled, claims 1 and 3 are amended to change the scope and breadth of the claims, and new claims 22-24 are added.

Claims 1-13 and 22-24 are pending in the instant application.

Priority

This application is a National Stage entry of PCT/EP2005/000215 filed on 12 January 2005 and claims priority to Germany foreign application 10 2004 002 001.9 filed on 14 January 2004. A certified copy of the foreign priority document in German has been received. No English translation has been received.

Information Disclosure Statement

The information disclosure statement (IDS) dated 25 February 2009 complies with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609. Accordingly, it has been placed in the application file and the information therein has been considered as to the merits.

Election/Restrictions

Claims 7, 8 and 10 were previously withdrawn from further consideration in the Office Action dated 24 October 2008 pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim.

Applicants request that withdrawn claims 7, 8 and 10 be examined as these claims recite additional ingredients and each explicitly requires the particulars of the elected method. Applicants are requested to note that Applicants elected for the absence of an inhibitor of hyaluronic acid degradation in the composition, and the absence of another glycosaminoglycan in the composition in the response filed on 23 September 2008. Furthermore, the search for these additional components would be an undue burden as they would require additional search employing additional search queries. As indicated in the Office Action dated 24 October 2008, the requirement was deemed proper and has been made FINAL.

New claims 22 and 24 are drawn to a non-elected species and are therefore withdrawn from further consideration pursuant to 37 CFR 1.142(b), there being no allowable generic or linking claim.

New claim 23 is drawn to the elected species, a viral skin disease which leads to wart formation, and will therefore be examined on its merits along with claims 1-6, 9 and 11-13 herein.

Rejections Withdrawn

Applicant's amendment, filed 24 February 2009, with respect to the rejections of claims 1-6, 9 and 11-13 under 35 USC § 112, first paragraph, for lack of enablement in preventing an inflammatory skin or mucous membrane disease, comprising administration to a subject in need thereof an effective amount of hyaluronic acid in

crosslinked form, has been fully considered and is persuasive because the amendment deletes the recitation "preventing" from the claim.

These rejections have been **withdrawn**.

Applicant's Remarks, filed 24 February 2009, with respect to the rejections of claims 1-6, 9 and 11-13 under 35 USC § 112, first paragraph, for lack of enablement in treating an inflammatory skin or mucous membrane disease, comprising administration to a subject in need thereof an effective amount of hyaluronic acid in crosslinked form, has been fully considered and is persuasive because Applicant has provided sufficient reasoning in their Remarks as to why they are enabled for the claimed invention.

These rejections have been **withdrawn**.

Applicant's amendment and Remarks, filed 24 February 2009, with respect to the rejections of claims 1-4, 9 and 11-13 under 35 USC § 103(a), as being unpatentable over U.S. Patent No. 5,914,322 to Falk *et al.*, in view of U.S. Patent No. 4,716,224 to Sakurai *et al.*, has been fully considered and is persuasive because the claim as amended requires that the method be administered intradermally, which is not taught in the combined teachings of the prior art.

These rejections have been **withdrawn**.

Applicant's amendment and Remarks, filed 24 February 2009, with respect to the rejections of claims 5 and 6 under 35 USC § 103(a), as being unpatentable over U.S.

Patent No. 5,914,322 to Falk *et al.*, in view of U.S. Patent No. 4,716,224 to Sakurai *et al.*, as applied to claims 1-4, 9 and 11-13, further in view of Wilkinson, has been fully considered and is persuasive because the claim as amended requires that the method be administered intradermally, which is not taught in the combined teachings of the prior art.

These rejections have been **withdrawn**.

In view of the cancellation of claims 14-21, all rejections made with respect to claims 14-21 in the previous Office Action are withdrawn.

These rejections have been **withdrawn**.

The following are new ground(s) or modified rejections necessitated by Applicants' amendment, filed on 24 February 2009, wherein the limitations in pending claims 1 as amended now have been changed; claims 2-6, 9, 11-13 and 23 depend from claim 1. The limitations in the amended claims have been changed and the breadth and scope of those claims have been changed. Therefore, rejections from the previous Office Action, dated 24 October 2008, have been modified and are listed below.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Section [0001]

Claims 1-4, 9, 11-13 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,914,322 to Falk *et al.* (herein referred to as the '322 patent, of record), in view of U.S. Patent No. 4,716,224 to Sakurai *et al.* (herein referred to as the '224 patent, of record), in view of U.S. Patent No. 6,455,066 B1 to Fischer *et al.* (herein referred to as the '066 patent, PTO-892, Ref. A).

The Falk '322 patent discloses that a therapeutically effective amount of hyaluronic acid in a composition is useful in the treatment of skin diseases and conditions by topically administering said composition to a subject. The topical composition may be used to treat diseases and conditions of the skin such as genital warts cervical cancer, human papilloma virus (HPV), and psoriasis, among others (column 7, lines 10-22; column 12, lines 28-39). The composition may be in any suitable form, such as a lotion or a cream (column 8, lines 61-62). As shown in Formulation (A), the weight of sodium hyaluronate is 661,600 (661 kDa) (column 13, lines 10-23). Examples 1-7 illustrate the use of the composition on human patients with lesions (Examples 1-3) or psoriasis (Example 7) (columns 25 and 26).

The Falk '322 patent does not explicitly teach that hyaluronic acid is in the crosslinked form or that it is administered intradermally.

The Sakurai '224 patent teaches that the hyaluronic acid typically administered to a subject is isolated and purified from a source and lacks the stringiness and viscoelasticity of hyaluronic acid typically found in the living body (column 1, lines 35-40). Moreover, hyaluronic acid is known to undergo enzymatic decomposition or non-enzymatic oxidation-reduction decomposition after being administered to a living body, especially at diseased sites (column 1, lines 41-44). Crosslinked hyaluronic acid, on the other hand, shows resistance to enzymatic decomposition or non-enzymatic oxidation-reduction decomposition (column 1, lines 54-59). Thus, crosslinked hyaluronic acid has a wide variety of medical and cosmetic uses (column 1, lines 61-63). The crosslinking index (percent of crosslinking) of the resultant crosslinked hyaluronic acid or salt thereof from a reaction, may be controlled by varying the molar ratio of the hyarluronic acid, or salt thereof, to the polyfunctional epoxy compound used for crosslinking (column 3, lines 3-6). The crosslinked hyaluronic acid may be used in skin cosmetics (column 4, lines 4-6), for application on, for example, shaving, cracking, and chappy skin (column 4, lines 28-30). The cosmetic containing crosslinked hyaluronic acid may be in the form of a cream, lotion, or hair cosmetic (column 4, lines 30-33). Example 8 illustrates the use of crosslinked hyaluronic acid on rabbits (column 10, lines 14-68).

The Sakurai '224 patent discloses crosslinked hyaluronic acid with varying degrees of crosslinking, as indicated by their crosslinking index. For example, crosslinked hyaluronic acids with a crosslinking index per 1000 repeating disaccharides in hyaluronic acid of 8.5, 7.5, 13 and 40 and disclosed in Examples 1-4, respectively. Moreover, the Sakurai '224 patent teaches that the degree of crosslinking may be

controlled by varying the molar ratio of the hyaluronic acid, or salt thereof, to the polyfunctional epoxy compound used for crosslinking (column 3, lines 3-6). Thus, it is considered that one of ordinary skill in the art would have the capabilities of adjusting their reaction to obtain a crosslinked hyaluronic acid with the desired percent of crosslinking.

The Fischer '006 patent provides the general teaching that drug administration via the skin is divided into two categories: 1) transdermal administration and 2) intradermal administration (column 1, lines 39-41). Transdermal administration involves transport through the skin and into the blood stream to treat systemic diseases (column 1, lines 41-43). On the other hand, intradermal administration is intended to impart a cutaneous effect, while keeping the pharmacological effects of the drug localized to the intracutaneous regions of drug penetration and deposition (column 1, lines 43-47). Ideally, intradermal absorption occurs with little or no systemic absorption or accumulation.

As such, it would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of the Falk '322 patent, concerning the treatment of skin diseases and conditions by administering a composition comprising a therapeutically effective amount of a non-toxic drug that inhibits prostaglandin synthesis with a therapeutically effective amount of hyaluronic acid, with the teachings of the Sakurai '224 patent, regarding the enzymatic decomposition and non-enzymatic oxidation-reduction of hyaluronic acid after being administered to a living body and how crosslinked hyaluronic acid is resistant to such decomposition, with the teachings of the

Fischer '006 patent, regarding the two routes for administering a drug to the skin, either transdermal or intradermal. One would have been motivated to combine the teachings in order to receive the expected benefit, as suggested in the Sakurai '224 patent, that crosslinked hyaluronic acid shows resistance to enzymatic decomposition or non-enzymatic oxidation-reduction decomposition (column 1, lines 54-59). Thus, one of ordinary skill in the art would know that the compound's half-life would be increased as it is no longer subjected to enzymatic and non-enzymatic oxidation-reduction decomposition. With regards to the route of administration, one of ordinary skill in the art would have been motivated to combine the teachings in order to receive the expected benefit, as suggested in the Fischer '006 patent, that intradermal administration imparts a cutaneous effect, while keeping the pharmacological effects of the drug localized to the intracutaneous regions of drug penetration and deposition, which ideally results in little or no systemic absorption or accumulation. Furthermore, as one of ordinary skill in the art is aware that the absorption, distribution, metabolism and excretion of a drug is critically influenced by its route of administration, it is considered within the capabilities of one of ordinary skill in the art to determine the best route of administration for a drug to achieve optimal treatment results.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Section [0002]

Claims 5 and 6 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,914,322 to Falk *et al.* (herein referred to as the '322 patent, of record), in view of U.S. Patent No. 4,716,224 to Sakurai *et al.* (herein referred to as the '224 patent, of record), in view of U.S. Patent No. 6,455,066 B1 to Fischer *et al.* (herein referred to as the '066 patent, PTO-892, Ref. A), as applied to claims 1-4, 9, 11-13 and 23, and further in view of chapter publication by Wilkinson (of record).

The teachings of the Falk '322 patent, the Sakurai '224 patent, and the Fischer '006 patent were as disclosed above in section [0001] of the claim rejections under 35 USC § 103.

The references do not teach a method wherein the composition comprises hyaluronic acid in both crosslinked and uncrosslinked form.

Wilkinson teaches the physiochemical factors involved in the transfer of drugs across membranes. Figure 1-6 discloses the therapeutic window in which a drug shows effectiveness (p. 25, first column). This window varies depending on factors such as the dosage, toxicity, absorption, distribution and its elimination half-life (p. 25, first column, first incomplete paragraph; p. 26, second column, first incomplete paragraph). In most clinical situations, drugs are administered in a series of repetitive doses or as a continuous infusion so as to maintain a steady-state concentration of drug associated with the therapeutic window (p. 26, first column, subheading "Maintenance Dose", first paragraph).

It would have been obvious to one of ordinary skill in the art at the time of the invention to combine the teachings of the Falk '322 patent, concerning the treatment of

skin diseases and conditions by administering a composition comprising a therapeutically effective amount of a non-toxic drug that inhibits prostaglandin synthesis with a therapeutically effective amount of hyaluronic acid, with the teachings of the Sakurai ‘224 patent, regarding the enzymatic decomposition and non-enzymatic oxidation-reduction of hyaluronic acid after being administered to a living body and how crosslinked hyaluronic acid is resistant to such decomposition, with the teachings of the Fischer ‘006 patent, regarding the two routes for administering a drug to the skin, either transdermal or intradermal, with the teachings of Wilkinson, regarding the therapeutic window of a drug and how it varies according to the drug's absorption, distribution and elimination characteristics. Since the Falk ‘322 patent teaches the treatment of skin diseases and conditions by administering a prostagladin synthesis inhibitor along with hyaluronic acid and the Sakurai '224 patent teaches that crosslinked hyaluronic acid is resistant to enzymatic and chemical degradation, as well as the use of crosslinked hyaluronic acid, then one would have been motivated to combine the teachings to make a composition comprising hyaluronic acid in both crosslinked and uncrosslinked form, in order to receive the expected benefit, that the combined composition would increase the therapeutic window of the drug. One of ordinary skill in the art would know that the uncrosslinked compound likely takes effect faster, but is also degraded faster, while crosslinked hyaluronic acid would remain in the bloodstream longer, thereby increasing the therapeutic window of effectiveness of the drug.

Thus, the claimed invention as a whole is *prima facie* obvious over the combined teachings of the prior art.

Conclusion

In view of the rejections to the pending claims set forth above, no claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to SCARLETT GOON whose telephone number is 571-270-5241. The examiner can normally be reached on Mon - Thu 7:00 am - 4 pm and every other Fri 7:00 am - 12 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Shaojia Anna Jiang/
Supervisory Patent Examiner, Art Unit 1623

/SCARLETT GOON/
Examiner
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